FDA U.S. FOOD & DRUG ADMINISTRATION

Technical Project Lead (TPL) Review of PMTA

New Tobacco Product[s] Subject of this Review[1]	
STN	PM0000634
Common Attributes	
Submission date	March 30, 2020
Receipt date	April 1, 2020
Applicant	Philip Morris Products S.A.
Product manufacturer	Philip Morris Products S.A.
Application type	Supplemental
Product category	Cigarette
Product subcategory	Non-combusted
Cross-Referenced Submission[s]	
PM0000634	PM0000479, (b) (4)
Supporting FDA Memoranda Relied Upon in this Review	
PM0000634	None
Recommendation	
Issue marketing granted order letter for the new tobacco product subject of this review.	

Technical Project Lead (TPL):

Priscilla Callahan-Lyon, M.D.
Senior Science Advisor
Office of the Director, Center for Tobacco Products

Signatory Decision:

☐ Concur with TPL recommendation and basis of recommendation

☐ Concur with TPL recommendation with additional comments (see separate memo)

☐ Do not concur with TPL recommendation (see separate memo)

Matthew R. Holman, Ph.D.
Director
Office of Science

[1] Tobacco product details, amendments, and dates provided in the Appendix. PMTA means premarket tobacco product application(s).

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1. EXECUTIVE SUMMARY

On April 1, 2020, FDA received a PMTA for the IQOS 3 device, to be used with the previously authorized Marlboro Heatsticks (regular, Smooth Menthol, and Fresh Menthol, PM0000424 – PM0000426). The applicant referenced the PMTAs for the Marlboro Heatsticks as well as for the IQOS 2.4 Holder and Charger, PM0000479. The previous PMTAs were granted marketing authorization April 30, 2019. The IQOS 3 Holder and Charger is similar in design to IQOS 2.4 and uses the same tobacco source (Marlboro Heatsticks).

Scientific review of the application found that the comparison between IQOS 2.4 and the proposed IQOS 3 device is appropriate. The applicant has provided adequate information on the manufacturing process and product quality controls that will help ensure that the IQOS 3 device is manufactured consistently and will meet the applicant's specifications. The aerosol from the IQOS 3 device has been evaluated and found to be comparable to that from use of the IQOS 2.4 device. No new exposures or risks for the new device were identified.

The IQOS 3 device is not marketed in the U.S.; however, the applicant has provided user information from the international marketing experience with IQOS 3 as well as consumer reports, complaint, published literature and product safety information. There were no new safety concerns or unexpected adverse experiences identified. The user information from international survey data found no evidence of increased uptake of IQOS by youth or young adults, and IQOS 3 seemed to be more accepted by consumers with a slightly decreased likelihood of dual use with cigarettes as compared to IQOS 2.4. There is no evidence the user population for IQOS 3 will be different from the population who use IQOS 2.4. Although the marketing information provided is not U.S. data, use patterns available for IQOS 2.4 within the U.S. have not raised new concerns regarding product use in youth and young adults. Given the product similarities, there is no evidence of increased risk for youth initiation and use for IQOS 3 as compared to IQOS 2.4.

There are no U.S. data for IQOS 3; however, the similarities in the product designs of IQOS 2.4 and IQOS 3, as well as the fact that the same Heatsticks are used in both devices, make it unlikely there are new concerns related to health effects, product quality, human factors, or product misuse for IQOS 3 as compared to IQOS 2.4. As the two devices have similar operating procedures, use the same tobacco sources, and produce comparable aerosols, FDA has no reason to believe the IQOS 3 device will result in different nicotine exposure, use patterns, user populations, or abuse liability.

The Agency determined that, given the modifications are mainly aesthetic, the projected market volume (Confidential Appendix 1) is similar to that of the original IQOS System, (b) (4) the environmental impacts of the new tobacco product IQOS 3 are considered in the original PMTA Environmental Assessment for IQOS 2.4. Specifically, the Agency did not identify any significant environmental impacts from the proposed and alternative actions.

In conclusion, none of the grounds specified in Section 910(c)(2) of the FD&C Act apply. Specifically, I find the following:

1. Permitting the marketing of the product is appropriate for the protection of the public health, as described in Section 910(c)(4) of the FD&C Act (subject to the labeling and advertising changes described below);

2. The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of the product do not fail to conform to the requirements in Section 906(e) of the FD&C Act;[2]
3. Based on a fair evaluation of all material facts, the proposed labeling is not false or misleading in any particular; and
4. The product does not fail to conform to a tobacco product standard in effect under Section 907 of the FD&C Act.

I recommend FDA grant marketing authorization for IQOS 3, PM0000634.

2. BACKGROUND

2.1. NEW TOBACCO PRODUCT

The applicant submitted information for the new tobacco product listed on the cover page and with more detail in the Appendix.

2.2. REGULATORY ACTIVITY

On April 1, 2020, FDA received one PMTA from Philip Morris Products S.A. FDA issued an Acceptance letter to the applicant on April 8, 2020. FDA issued a Filing letter to the applicant on April 20, 2020.

FDA sent a Deficiency letter to Philip Morris Products S.A. on August 13, 2020, requesting additional information needed to complete the review. The applicant responded on August 27, 2020. Information in this amendment, PM0000907, is considered in this review.

Refer to the Appendix for a complete list of amendments received by FDA.

2.3. SCOPE OF REVIEW

This review captures all compliance and scientific reviews completed for the new tobacco product subject of this review. (b) (4) was reviewed by the chemistry review team; the information is sufficient for this PMTA. The information in (b) (4) was included in the PMTA; therefore, a separate written review of (b) (4) was not needed. (b) (4)

Table 1. Disciplines reviewed

Discipline	Reviewer(s)	Review Date
Engineering	Pritesh Darji	8/11/2020
Chemistry	Yuan-Wei (David) Nei	8/13/2020
Medical	Lester Lacorte	8/12/2020
Environmental	Shannon Hanna	8/12/2020, 10/6/2020

Table 2. Consults

OCE – BIMO	Tara Singh	7/9/2020
OCE – DEM	Abraham Agyapong	6/17/2020
OCE – DPAL	Melissa View	8/12/2020, 10/6/2020

[2] FDA has not yet promulgated any regulations under Section 906(e) of the FD&C Act.

3. SCIENTIFIC REVIEW

3.1. COMPARISON PRODUCT

3.1.1. Discipline key findings

- The applicant compared IQOS 3 with previously authorized IQOS 2.4.
- The applicant compared 57 aerosol HPHC yields and four additional aerosol constituents generated from the monitor Heatsticks using the IQOS 3 system and the previously authorized IQOS 2.4 system. (b) (4) The applicant states the monitor Heatstick is equivalent to the regular Marlboro Heatsticks marketed in the U.S. The applicant also compared the IQOS aerosol yields to measured mainstream smoke HPHCs of Kentucky reference cigarettes 3R4F and 1R6F.
- The applicant compared the IQOS 3 System Holder and Charger to the authorized IQOS 2.4 System in terms of the safety profile and Adverse Event (AE) proportion and distribution using post-market consumer reports, global AE data, and published literature. The applicant-submitted data indicates the IQOS 3 and IQOS 2.4 products are comparable and have similar characteristics with respect to their reported safety and health effects (AE) profile.

3.1.2. Synthesis

This supplemental PMTA for the IQOS 3 device appropriately compares the new proposed device to the previously authorized IQOS 2.4 device. The application includes data demonstrating that using the authorized Marlboro Heatsticks in the IQOS 3 device produces aerosol that is equivalent to that produced by the authorized IQOS 2.4 device. The IQOS 3 device is not available in U.S. markets but is marketed internationally; the applicant has provided information from post-market consumer report databases, global AE data, and published literature that do not demonstrate new or unexpected AEs related to use of IQOS 3 with the authorized Marlboro Heatsticks. The applicant has demonstrated that using the IQOS 3 device with the Marlboro Heatsticks is comparable to use of the authorized IQOS 2.4 device with the same Heatsticks.

3.2. PRODUCT CHARACTERIZATION

3.2.1. Discipline key findings

Product design and composition

- The IQOS 3 system consists of a holder that heats tobacco sticks (Marlboro Heatsticks) and a charger that recharges the holder after each Heatstick use. The IQOS 3 system has the following changes from the previously authorized IQOS 2.4 system:
    - New side-opening design on the charger (for insertion of the holder)
    - New magnetic charging connector on the holder
    - New LED indicator light design
    - New haptic feature
    - (b) (4)

- There were two reported AEs that initially appeared to have been related to product quality issues; however, after further review and analysis, it is unlikely that either of these events were associated with the IQOS 3 device.

Manufacturing

- The applicant described the manufacturing process for IQOS 3 including the assembly of the holder and charger printed circuit boards (PCBs), final assembly of the holder and charger, and packaging of the IQOS 3 device. Manufacturing of IQOS 3 System is performed by two companies, both owned by (b) (4) (b) (4) Both companies are located in (b) (4) .
- Assembly of the IQOS 3 System consists of (b) (4) :
  - (b) (4)
- The applicant has provided sufficient details of the assembly processes, in-process controls, and product release testing at each assembly process for the IQOS 3 System. The described manufacturing processes and control strategies are appropriate for ensuring consistency in the product production.
- No manufacturing inspections were conducted as part of this review.

Product stability

- There were no stability data included in the submission. As this supplemental PMTA is for a device, no stability data is necessary.

Product test data

- Test data provided by the applicant support the provided battery specifications and range limits and adequately characterize battery performance. In addition, the applicant submitted thermal cleaning profile specifications and data describing droplet size distribution.
- The PMI-58 study showed that aerosol HPHC data from the new IQOS 3 System and the previously authorized IQOS 2.4 System using monitor Heatsticks were analytically equivalent (b) (4) Additionally, aerosol HPHC yields for the new IQOS 3 System with monitor Heatsticks were lower compared to mainstream smoke (MSS) HPHC yields from the 3R4F reference cigarette.
- The FDA-18 study showed that aerosol HPHC data generated from the new IQOS 3 System using commercially available Heatsticks were lower than MSS HPHC data generated from the 1R6F reference cigarette.
- The applicant provided data for four additional constituents: 3-chloro-1,2-propondiol, furfural, 2-furanmethanol, and glycidol. Aerosol yields for these four constituents produced by the IQOS 3 System using monitor Heatsticks, generated from (b) (4) , were higher than those from the reference 1R6F cigarette. This is consistent with the results observed with the previously authorized IQOS 2.4 system, PM0000479; the aerosol generated by the IQOS 3 System and the previously authorized IQOS 2.4 System were analytically equivalent for all four constituents.

3.2.2. Synthesis

As TPL, I agree with the engineering and chemistry conclusions that this PMTA contains sufficient information to characterize the product design and adequate processes and controls to help ensure that the product meets the manufacturer's specifications.

3.3. ABUSE LIABILITY

3.3.1. Discipline key findings

There were no specific data related to nicotine pharmacokinetics, withdrawal, craving, or subjective effects included in this application.

3.3.2. Synthesis

There are no new data specifically related to abuse liability in this supplemental PMTA. The IQOS 3 device operates in a similar manner and uses the same Marlboro Heatsticks as the previously authorized IQOS 2.4 device. The aerosol from the IQOS 3 device has been evaluated and found to be comparable to that from use of the IQOS 2.4 device. As the two devices have similar operating procedures, use the same tobacco sources, and produce comparable aerosols, FDA has no reason to believe the IQOS 3 device will result in different nicotine exposure, use patterns, user populations, or abuse liability.

3.4. USER POPULATIONS

3.4.1. Discipline key findings

This PMTA did not include new data related to product use or user populations for IQOS in the U.S. The applicant provided results of IQOS use behaviors based on surveys conducted among IQOS owners in 5 non-U.S. countries (Germany, Japan, Italy, South Korea, and Switzerland). The results include information on average daily consumption (measured as Heatsticks/day) and use patterns and are stratified by gender and age for each country. In each of these countries, multiple IQOS products are available for purchase including IQOS 2.4, IQOS 2.4P (this version superseded IQOS 2.4 in international markets), and IQOS 3. In general, more survey participants owned only the IQOS 3 device than owned multiple devices; i.e., both IQOS 2.4/IQOS 2.4P and IQOS 3. In addition, of those surveyed, owners of IQOS 3 were more likely to predominantly or exclusively use this device as compared to using multiple IQOS types or dual use of IQOS and cigarettes. The self-reported data show that in September 2019, among IQOS owners who completed the survey, exclusive use of IQOS 3 across these five countries was ~60%.

Labeling and advertising

The initial supplemental PMTA did not include full copies of all the proposed product labeling, including color variations. Additional information was submitted by the applicant on August 27, 2020. The Division of Promotion, Advertising, and Labeling (DPAL) in the Office of Compliance and Enforcement (OCE) conducted a supplementary review of the label and labeling and had no concerns regarding the labeling submitted.

3.4.2. Synthesis

The marketing and use patterns for IQOS 3 in other countries does not necessarily reflect or predict initiation or user behavior in the U.S. It is helpful to note that IQOS 3 seems to be accepted by tobacco users in other countries and some of the users report switching completely to IQOS (as opposed to dual use with cigarettes). However, the data are quite limited. The survey only included those willing to provide information and who had

purchased at least one IQOS system. In addition, panelists who owned IQOS devices other than IQOS 2.4, 2.4P or IQOS 3 (e.g., IQOS 3 Multi – another version available in some countries) or those who own other heated tobacco products were excluded. Youth and young adults < age 24 years were grouped together making it impossible to determine the rate of youth interest and initiation/product purchase; however, mean age of the IQOS users in all the countries was ~ 40 years. FDA has no reason to believe the marketing and use patterns in the U.S. for IQOS 3 will be significantly different from those for IQOS 2.4. The postmarket restrictions imposed on IQOS 2.4 would also be imposed on IQOS 3; these restrictions will prevent acquisition of IQOS 3 by consumers below legal age. These international data may not reflect the way IQOS 3 would be used in the U.S. Tobacco product regulations and product availability vary from country to country. Additionally, the advertising and marketing plans used by manufacturers varies depending on the local market conditions and regulations. All of these factors limit the usefulness of this information in supporting the PMTA.

3.5. TOXICANT EXPOSURE

3.5.1. Discipline key findings

The nonclinical data provided in this application demonstrate that the aerosol generated with the IQOS 3 device when using Marlboro Heatsticks is comparable to that generated with the IQOS 2.4 device using the same Heatsticks. This supplemental PMTA relies on the nonclinical data submitted for the IQOS 2.4 (PM0000479) and the Marlboro Heatsticks (PM0000424 – PM0000426).

3.5.2. Synthesis

The IQOS 3 device operates in a similar manner and uses the same Marlboro Heatsticks as the authorized IQOS 2.4 device. The aerosol from the IQOS 3 device has been found to be comparable to that from use of the IQOS 2.4 device. As the two devices have similar operating procedures, use the same tobacco source, and produce comparable aerosols, there is no reason to believe the IQOS 3 device will result in different toxicant exposures.

3.6. HEALTH EFFECTS

3.6.1. Discipline key findings

BIMO inspection findings

- No inspections were conducted.

Short and long-term health effects (clinical and observational)

- No new health effects or different health risks were reported for the IQOS 3 System Holder and Charger to raise additional product concerns.

Likelihood and effects of product misuse

- The application provided Safety Warnings and Instructions for IQOS 3 to address human use factors, mitigate potential product malfunction, and reduce the risk of injury.
- Accidental secondhand exposure data for IQOS 3 is limited in the applicant-submitted published research.
- The overall health risks appear to be similar for IQOS 2.4 and IQOS 3.

- There were no product engineering and design features of concern for IQOS 3.
- The likelihood of and effects from product misuse are expected to be comparable for the IQOS 2.4 and IQOS 3 Systems.
- The user profile and characteristics and product use behaviors are expected to be similar across IQOS products.

Adverse experiences

- The AE profile appears similar for the IQOS 3 System compared with the authorized IQOS 2.4 System. The applicant provided non-U.S., spontaneous consumer-reported AE Reports from the PMI Global Safety Database. No human clinical studies were provided in this supplemental application. There are limited specific data on product use patterns; e.g., dual use, incomplete switching, complete switching, and the data provided are survey results from use of IQOS 3 in non-U.S. markets. This limits the analysis of AEs from real-world use of the IQOS 3 System with other concomitant tobacco product use.
- Data from the PMI global safety database indicate that both versions of the IQOS System have similar proportions and numbers of AEs in the most frequently reported System Organ Class (SOC). Specific health effect data from U.S.-based product users is limited as the IQOS 3 System is not commercially available in the U.S.
- A search of CTP's Safety Reporting Portal (SRP) found three reports that contained the word "IQOS" submitted between 1/1/2014 and 6/24/2020. All of these were submitted from outside the U.S. and the specific IQOS device is not identified. There was one report on the PMI Tobacco Heating System 2.2 and one that named "heets." None of the information found in the SRP indicates new or unexpected AEs associated with IQOS 3.

3.6.2. Synthesis

The applicant reports the total number of IQOS users worldwide is > 12.4 million and estimates that ~24% of current IQOS users use the IQOS 3 system. As described in Section 3.4.1, the applicant included a user survey describing IQOS use behavioral data from IQOS owner panels in Germany, Japan, Italy, South Korea, and Switzerland. The applicant also provided information from their consumer product safety database and updates from published literature related to use of IQOS products.

There are limited data specifically related to use of IQOS 3; however, the provided information does not indicate any new or unexpected AE signals in the literature, the global database, or the consumer reports. There are no U.S. data for IQOS 3; however, the similarities in the product designs of IQOS 2.4 and IQOS 3, as well as the fact that the same Heatsticks are used in both devices, make it unlikely there are new concerns related to health effects, product quality, human factors, or product misuse for IQOS 3 as compared to IQOS 2.4.

3.7. POPULATION AND PUBLIC HEALTH

3.7.1. Discipline key findings

The population health information included in this supplemental PMTA is related to the survey data described in Section 3.4.1.

3.7.2. Synthesis

As noted above, the application does not include specific information on use of IQOS 3 in the U.S. The submitted product use information, including product initiation, use patterns, populations, dual use, switching behaviors, etc., are the survey results from non-U.S. countries and do not necessarily translate to behaviors in the U.S. where tobacco regulation and product availability is different.

This application is for a new IQOS device which will be used with the same Heatsticks authorized for use in the IQOS 2.4 device. As the product design and characteristics are similar, the tobacco source (Marlboro Heatsticks) is unchanged, and the aerosol produced from using the Heatsticks in the two devices is comparable, there is no reason to believe the impact on population health will be different for IQOS 3 as compared to IQOS 2.4. In fact, the survey data (non-U.S.) submitted by the applicant indicates there may be an increased likelihood of complete switching for combusted cigarette users who purchase an IQOS 3 device. Although the non-U.S. data may be of limited use for supporting the PMTA, this survey data supports the conclusion that combusted cigarette users who switch to IQOS 3 should see health benefits similar to the benefits of switching to IQOS 2.4.

There is no evidence the user population for IQOS 3 will be different from the population who use IQOS 2.4. The survey data also show no evidence of increased youth and young adult initiation of IQOS 3 use in international markets. This is not U.S. data, but use patterns available for IQOS 2.4 within the U.S. have not raised new concerns regarding product use in youth and young adults. Given the product similarities, there is no evidence of increased risk for youth initiation and use for IQOS 3 as compared to IQOS 2.4.

3.8. STATUTORY REQUIREMENTS

3.8.1. Public health conclusion

Based on the findings and evaluations discussed in Sections 3.1-3.7, permitting marketing of the IQOS 3 device as described by the applicant for use with the authorized Marlboro Heatsticks is determined to be appropriate for the protection of the public health (APPH). The proposed product labeling is not false or misleading.

3.8.2. Tobacco product manufacturing practices

The methods used in, and the facilities or controls used for, the manufacture, processing, and packing of these products do not fail to conform to the requirements in Section 906(e) of the FD&C Act. The PMTA contains sufficient information to characterize the product design and adequate processes and controls to help ensure that the product meets the manufacturer's specifications.

3.8.3. Product standards

There are no applicable product standards for this PMTA.

4. ENVIRONMENTAL DECISION

4.1. DISCIPLINE FINDINGS

Potential impacts of the proposed action and no action, from product manufacturing, use, and disposal, are discussed in the Environmental Assessment (EA) for the original IQOS System PMTA (STNs PM0000424, PM0000425, PM0000426 and PM0000479). The tobacco product in this EA is

slightly modified as compared to the tobacco product in the original PMTA with the above-mentioned differences. The Agency determined that, given the modifications are mainly aesthetic, the projected market volume (Confidential Appendix 1) is similar to that of the original IQOS System, and that (b) (4) , the environmental impacts of the new tobacco product are considered in the original PMTA EA. Specifically, the Agency did not identify any significant environmental impacts from the proposed and alternative actions.

4.2. ENVIRONMENTAL CONCLUSION

A finding of no significant impact (FONSI) was signed by Luis G. Valerio, Jr., on October 6, 2020. The FONSI was supported by an environmental assessment prepared by FDA on October 6, 2020.

5. CONCLUSION AND RECOMMENDATION

Based on our review of your PMTA, we determined that permitting marketing of the new tobacco product, as described in your application and specified in Appendix, Table 3, is appropriate for the protection of the public health. The issuance of this marketing granted order confirms that you have met the requirements of section 910(c) of the FD&C Act and authorizes marketing of your new tobacco product. Under the provisions of section 910, you may introduce or deliver for introduction into interstate commerce the tobacco product, in accordance with the marketing order requirements outlined in this order, including all appendices. Periodic reporting is required on a quarterly basis. See Appendix B for additional information on reporting requirements.

FDA has examined the environmental effects of finding the new tobacco product appropriate for the protection of the public health and made a Finding of No Significant Impact (FONSI).

A marketing granted order should be issued for the new tobacco product subject of this review, as identified on the cover page of this review.

6. APPENDIX

Table 3. New tobacco product

Common Attributes	
Submission date	March 30, 2020
Receipt date	April 1, 2020
Applicant	Philip Morris Products S.A.
Product manufacturer	Philip Morris Products S.A.
Product category	Cigarettes
Product subcategory	Non-Combusted
Attributes[3]	**New Tobacco Product**
STN	**PM0000634**
Product name	IQOS 3 device[4]
Package type	Box
Package quantity	1 Holder, 1 Charger
Characterizing flavor	None[5]
Length	92.25 mm (Holder) 114.90 mm (Charger)
Diameter	14.40 mm (Holder) (smallest) 14.90 mm (Holder) (largest area with protruding button)
Ventilation	Not Provided
Source of energy	Electric (rechargeable battery)
Additional property	Thickness: 23 mm (Charger) Width: 46.35 mm (Charger) Battery Capacity: (b) (4) (Holder) Battery Capacity: (b) (4) (Charger)

Table 4. Amendments

Submission Date	Receipt Date	Amendment	Applications being amended	Reviewed	Status	Brief Description
August 27, 2020	August 27, 2020	PM0000907	All[6]	Yes	Active	Response to August 13, 2020 FDA Information Request

[3] We interpret package type to mean container closure system and package quantity to mean product quantity within the container closure system, unless otherwise identified.
[4] Brand/sub-brand or other commercial name used in commercial distribution.
[5] Provided as part of product labeling
[6] This amendment applies to all STN subject of this review.

Priscilla Callahan-Lyon, M.D.

6.1. MARKETING GRANTED ORDER APPENDICES

6.1.1. Appendix A: Postmarket Recordkeeping and Retention

Under section 910(f) of the FD&C Act, this order requires that you establish and maintain the records listed below. At any time during the retention period described in this order, FDA may request that you provide any of the documents described below. In addition, under section 704 of the FD&C Act, FDA may inspect your establishment(s) and request to inspect any record(s) described below.

The following records must be retained according to the retention periods described below. These records must be legible, in English, and available for inspection and copying by officers or employees duly designated by the Secretary, upon request.

Record	Description	Retention Period
Prior PMTAs	Each PMTA submitted prior to marketing orders	4 years from the date that FDA issued the marketing order
Postmarket reports	Postmarket reports, including periodic and adverse experience reports as described in this order	4 years from the date the report was submitted to FDA or until FDA inspects the records, whichever occurs sooner
Correspondence with FDA	Correspondence with FDA pertaining to each authorized product	4 years from the date of distribution of the last batch of each product subject to this order
Study data	Nonclinical or clinical study documentation including: • Source data; • Study protocols (including statistical analysis plan) and amendments showing the dates and reasons for each protocol revision; • Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approvals or nonapprovals; • Informed consent forms; • Correspondence with study monitors/investigators/contract research organizations/sponsors/IRB/IEC; • Investigator financial disclosure statements; • Progress reports; • Monitoring reports; • Adverse experience reports; • Case report forms/subject diaries/medical records/laboratory reports; • Subject data line listings/observations records; • Test article accountability records; • Study results/protocol summaries/study reports; and • Certifications and amendments to certifications	4 years from the date of the order or 4 years from the conclusion of the study, whichever occurs later
Manufacturing records	Records pertaining to the manufacture, in process and release testing, production process (including any changes to the process, facility, or controls),	4 years from the date of distribution of each batch of each product subject to this order

Record	Description	Retention Period
	packaging, storage, and stability monitoring and testing (including protocol and results) Records and reports of all manufacturing deviations, investigations, and corrective and preventive actions including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding and distribution; and any deviation that may affect the characteristics of each final product[7] For products that have been distributed, if a deviation occurs that you determine presents a reasonable probability that the tobacco product contains a manufacturing or other defect not ordinarily contained in tobacco products on the market that would cause serious, adverse health consequences or death you are required to report the deviation to FDA within 15 calendar days of identification.	
Sales and/or distribution records	A list of distributors and retailers of the products, including brick-and-mortar and digital[8] (including internet/online and mobile) Any available information (not to include personally identifiable information) about product purchasers, such as purchasers' demographics (e.g., age, gender, race/ethnicity, geographic region) and previous or current use of other tobacco products (i.e., dual use) With respect to individuals under the legal purchasing age, policies and procedures regarding restrictions on access to the products, including purchaser age and identity verification processes	4 years from the date of distribution of each batch of each product subject to this order
Complaints	Records pertaining to any and all complaints associated with the tobacco product that is the subject of this order; such records may also include your analysis of those complaints	4 years from the date of distribution of each batch of each product subject to this order
Health hazard analysis	Health hazard analyses, if performed voluntarily or directed by FDA	4 years from the date of distribution of each batch of each product subject to this order
Labeling	Specimens of all labeling (including all labeling variations, such as those reflecting different required warnings), labels, inserts/onserts, instructions, and other accompanying information	4 years from the date of initial dissemination to the public
Advertising, marketing and promotional materials and plans	Copies of all advertising, marketing, and/or promotional materials published, disseminated to consumers, or for use in engaging or communicating with consumers	4 years from the date of initial dissemination to the public or implementation

[8] For the purposes of this order, here and throughout the document, "digital" includes internet/online and mobile.

Record	Description	Retention Period
	Copies of all advertising and marketing plans including strategic creative briefs and paid media plans, by channel and by product, dollar amount(s) and flighting of such plans, by channel and by product, including any: • Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys; • Targeting of specific group(s) by age-range(s), including young adults, ages 21-24, and other demographic or psychographic characteristics that reflect your intended audience(s), including the source of such data; • With respect to individuals under the legal purchasing age, actions taken to restrict access to the product and limit exposure to the products' labeling, advertising, marketing, and promotion, or other consumer directed activities; • Use of owned, earned, shared, or paid media to create labeling for, advertise, market, or promote the products; • Use of partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the products; • Consumer engagements – whether conducted by you, on your behalf, or at your directions - including events at which the products were demonstrated and how access was restricted to individuals at or above the legal purchasing age; or • Use of public relations or other communications outreach to create labeling for, advertise, market, or promote the products Copies of all records pertaining to the actual delivery of advertising impressions, including media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region), and all post-launch delivery-verification reports submitted to you from an accredited source, by channel, by product, and by audience demographics Policies and procedures for real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to individuals under the minimum legal purchasing age, including documentation of such monitoring activities and	

Record	Description	Retention Period
	implementation of corrective and preventive measures	
Formative consumer research	Copies of any formative research studies conducted among any audiences, in the formation of the labeling, advertising, marketing, or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing	4 years after the studies are completed
Consumer evaluation research	Copies of any consumer evaluation research studies conducted among any audiences to determine the effectiveness of the labeling, advertising, marketing, and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including copies of the stimuli used in testing	4 years after the studies are completed
Contractual agreements	Copies of any contractual agreements regarding the creation or dissemination of the products' labeling, advertising, marketing, or promotional materials, including, for example, in print media, online or through digital platforms (e.g., social media and mobile applications), such as influencers, bloggers, and ambassadors, on your behalf, or at your direction	4 years from the date of the contract termination

6.1.2. Appendix B: Postmarket Reporting

I. Periodic Reporting

Under section 910(f) of the FD&C Act, this order requires that you submit the following periodic reports to FDA on a quarterly basis for a period of two years beginning six months from the date of this order or when the next report for PM0000479 is submitted, whichever is first. For each three-month reporting period, these periodic reports must include:

- A single submission with a cover letter that includes the following subject line: **PERIODIC REPORT for PM0000634**. The cover letter should include the STN(s) and corresponding tobacco product name(s), applicant name, date of report, and reporting period.
- A summary of U.S. sales and distribution of the tobacco products, including total U.S. sales reported in dollars, units, and volume, and broken down by U.S. census region, major retail markets, and channels where the products are sold (e.g., convenience stores, food and drug markets, big box retailers, digital platforms, tobacco specialty shops, company-owned stores). This summary must also be broken down by product (e.g., specific HeatStick flavor).
- Data on product purchasers. Report any data collected about new purchasers, those who have switched tobacco products, and/or multiple product users. The results must be broken down by purchaser demographics (e.g., age, gender, race/ethnicity, geographic location) and must not include personally identifiable information.

Under section 910(f) of the FD&C Act, this order also requires that you submit the periodic reports to FDA on a quarterly basis beginning six months from the date of this order or when the next report for PM0000479 is submitted, whichever is first. For each three-month reporting period, these periodic reports must include:

- A cover letter that includes the following text in your subject line: **PERIODIC REPORT for PM0000634.** The cover letter should include the STN(s) and corresponding tobacco product name(s), firm name, date of report, reporting period.
- An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under). This analysis must be verified against post-launch delivery-verification reports submitted to you from an accredited source.
- A summary of media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to youth, ages 17 and under, and including a summary of implementation of any corrective and preventive measures.

Under section 910(f) of the FD&C Act, this order require that you submit the following postmarket reports to FDA on an annual basis, beginning twelve months from the date of the order[9] to help FDA determine whether continued marketing of each new tobacco product is appropriate for the protection of the public health or whether there is or may be grounds for withdrawing or temporarily suspending such order. For the 12-month reporting period, the report must include:

- A single submission with a cover letter that includes the following subject line: **PERIODIC REPORT for PM0000634.** The cover letter should include the STN(s) and corresponding tobacco product name(s), applicant name, date of report, reporting period, and marketing status outside the United States;

[9] The Annual Report for PM0000634 can be submitted with the Annual Report for PM0000479 beginning April 2021.

- A summary of how the marketing of the tobacco products continues to be appropriate for the protection of public health, which includes:
    - A status report of ongoing studies and a summary of completed studies about the tobacco products conducted by you, or on your behalf.
    - A summary of significant findings in publications not previously reported and full copies of the articles. This must include any new scientific data (published or otherwise) on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults.
    - A summary of reported adverse experiences for the tobacco products, which includes a listing of all adverse experiences, including the serious and unexpected adverse experiences previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the products including nature, frequency, and potential aggravating factors.
    - A summary of U.S. sales and distribution of the tobacco products, not previously submitted, including total U.S. sales reported in dollars, units, and volume, and broken down by U.S. census region, major retail markets, and channels where the products are sold (e.g., convenience stores, food and drug markets, big box retailers, digital platforms, tobacco specialty shops, company-owned stores). This summary must also be broken down by product.
    - Data on product purchasers not previously submitted. Report any data collected about new purchasers, those who have switched tobacco products, and/or multiple product users. The results must be broken down by purchaser demographics (e.g., age, gender, race/ethnicity, geographic location) and must not include personally identifiable information.
    - A summary of the implementation and effectiveness of your policies and procedures regarding verification of the age and identity of purchasers of the products.
    - A summary of the implementation and effectiveness of your policies and procedures regarding restrictions on youth access to the products.
    - A description of each change made to the manufacturing process, facilities, or controls during the reporting period including:
        - A comparison of each change to what was described in the PMTAs;
        - The rationale for making each change; and
        - A certification that the reported change did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke or aerosol constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of the tobacco products and the basis for concluding that each manufacturing change did not result in any modification to the products.
    - A summary of all manufacturing deviations, investigations, and corrective and preventive actions, including, but not limited to, those deviations associated with processing, testing, packing, labeling, storage, holding, and distribution and indicate any deviation(s) that may affect the characteristics of the products.
    - All final printed labeling, including all labeling variations not previously submitted, including the date the labeling was first disseminated and the date when the labeling was discontinued, and a description of all changes to the labeling. The labeling must include all the panels and be presented in the actual size and color with legible text. The labeling must include labels, inserts/onserts, instructions, and any other accompanying information or materials for the products.

- All final full-color advertising, marketing, and/or promotional materials, published, disseminated to consumers, or for use in engaging or communicating with consumers not previously submitted, along with the original date such materials were first disseminated and the date they were discontinued, and a description of all changes to the materials. The materials must include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5" x 11" piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read lettering clearly. If resizing the advertisement does not allow for text to be read easily, the text may be provided separately and referenced.
- A summary of all formative consumer research studies conducted – whether by you, on your behalf, or at your direction – among any audiences, in the formation of new labeling, advertising, marketing, and/or promotional materials, including qualitative and quantitative research studies used to determine message effectiveness, consumer knowledge, attitudes, beliefs, intentions and behaviors toward using the products, and including the findings of these studies and copies of the stimuli used in testing.
- A summary of all consumer evaluation research studies conducted – whether by you, on your behalf, or at your direction – among any audiences, to determine the effectiveness if labeling, advertising, marketing and/or promotional materials and any shifts in consumer knowledge, attitudes, beliefs, intentions, and behaviors toward using the products, and including the findings of these studies and copies of the stimuli used in testing.
- A summary of the creation and dissemination of the products' labeling, advertising, marketing, and/or promotional materials – whether conducted by you, on your behalf, or at your direction – not previously submitted, including a list of all entities involved and a description of their involvement, including a description of contractual agreements with such entities.
- A description of the implementation of all advertising and marketing plans, including strategic creative briefs and paid media plans – whether conducted by you, on your behalf, or at your direction – by channel and by product, and the dollar amount(s) and flighting of such plans, by channel and by product, including a description of any:
  - Use of competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys;
  - Targeting of specific adult audiences by age-range(s), including young adults, ages 18-24, and other demographic and/or psychographic characteristics that reflect the intended target audience, including a list of all data sources used to target advertising and marketing plans and media buys;
  - Actions taken to restrict youth-access and limit youth-exposure to the products' labeling, advertising, marketing, and/or promotion;
  - Use of owned, earned, shared, and/or paid media to create labeling for, advertise, market, and/or promote the products;
  - Use of partners, influencers, bloggers, and/or brand ambassadors to create labeling for, advertise, market, and/or promote the products;
  - Consumer engagements – whether conducted by you, on your behalf, or at your direction – including events at which the products were demonstrated; and/or
  - Use of earned media and/or public-relations outreach to create labeling for, advertise, market, and/or promote the products; including the original date such

plans were first used and the date they were discontinued, and a description of all changes to such plans since the last periodic report, by channel and by product.

- An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a breakout by age-group (i.e., adults, ages 25+; young adults, ages 18-24; and youth, ages 12-17 and ages 11 and under), not previously submitted. This analysis must be verified against post-launch delivery-verification reports submitted to you from an accredited source.
- A summary of media tracking and optimization, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic location), including a summary of real-time digital media monitoring to identify, correct, and prevent delivery of advertising impressions to youth, ages 17 and under, and including a summary of implementation of any corrective and preventive measures, not previously submitted.

II. Serious and Unexpected Adverse Experiences Reporting

Under section 910(f) of the FD&C Act, this order requires that you report to the FDA all adverse experiences that are both serious and unexpected and your analysis of the association between the adverse experience and each new tobacco product **within 15 calendar days** after the report is received by you. These experiences may become known to you through a customer complaint, request, or suggestion made as a result of an adverse experience, a manufacturing deviation analysis, tobacco product defect, or failure reported to you; or identified in the literature or media. Your information should be submitted with a cover letter that includes the following subject line: **SERIOUS UNEXPECTED ADVERSE EXPERIENCE REPORT for PM0000634**.

For purposes of reporting under this order, serious adverse experience means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption in the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of reporting under this order, unexpected adverse experience means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to each tobacco product as described in the PMTA and other relevant sources of information, such as product labeling and postmarket reports;
- The expected natural progression of any underlying disease, disorder, or condition of the persons(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or

- The results of nonclinical laboratory studies.

III. Notifications

Under sections 910(c)(1)(B) and 910(f) of the FD&C Act, this order also requires that for the first six months after the date of your marketing granted order you provide FDA a notification of all labeling, advertising, marketing, and/or promotional materials for which you plan on disseminating to the public or using to engage or communicate with consumers. These notifications are not for pre-approval but are required so that FDA can have timely access to your marketing plans and materials, and if needed, provide you advisory comments, including any concerns about their possible impact on youth appeal and tobacco use initiation and, on the finding that continued marketing of your product is appropriate for the protection of the public health. Failure to comment on your 30-day notifications does not mean that FDA determined that your materials are compliant. You may begin disseminating the materials 30 days after providing notification to FDA. This notification must be received by FDA **at least 30 days** prior to dissemination, which includes but is not limited to the publication, dissemination to consumers, or use in engaging or communicating with consumers of such materials.

Each 30-day notification must include:

1. A single submission with a cover letter that includes the following subject line: **30-DAY NOTIFICATION for PM0000634**. The cover letter should include the STN(s) and corresponding tobacco product name(s), applicant name, date of notification, and planned dissemination date;

2. Full-color copies of all such labeling, advertising, marketing, and/or promotional materials for the product. The materials must be legible, include all panels where applicable (e.g., print ads, point of sale signs) and reflect the actual size and colors used. For any materials that would not fit on an 8.5" x 11" piece of paper, you may resize and submit electronic versions of such materials in a format that FDA can review and with sufficient resolution to allow FDA to read all lettering clearly. If resizing the advertisement does not allow for text to be read easily, the complete text must be provided separately and clearly referenced.

3. All advertising and marketing plans, including strategic creative briefs and paid media plans, by channel and by product, dollar amount(s) and flighting of such plans, by channel and by product, including any plans to:
    a. Use competent and reliable data sources, methodologies, and technologies to establish, maintain, and monitor highly targeted advertising and marketing plans and media buys, including a list of all data sources used to target advertising and marketing plans and media buys;
    b. Targeting specific group(s) by age-range(s), including young adults, ages 21-24, and other demographic or psychographic characteristics that reflect your intended audience, including a list of all data sources used to target advertising and marketing plans and media buys;
    c. With respect to individuals below the minimum purchasing age, actions taken to restrict access and exposure to the products' labeling, advertising, marketing, or promotion;
    d. Use owned, earned, shared, or paid media to create labeling for, advertise, market, or promote the product;
    e. Use partners, influencers, bloggers, or brand ambassadors to create labeling for, advertise, market, or promote the product;

f. Conduct consumer engagements – whether by you, on your behalf, or at your direction – including events at which the products will be demonstrated and how access will be restricted to individuals at or above the legal purchasing age; or
g. Use public-relations or other communications outreach to create labeling for, advertise, market, or promote the product.

6.1.3. Appendix C: Marketing Requirements

Under section 910(c)(1)(B) of the FD&C Act, this order requires:

- For any **digital sales** – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, to prevent the sale of the product to individuals who are under the federal minimum legal age to purchase tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in your **owned digital properties** (e.g., your company-owned, consumer-directed, product-branded website(s) and/or mobile applications) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of independent age- and identity-verification service(s) that compare customer information against independent, competent, and reliable data sources, such as public records, at the first point of access to such properties in order to restrict access to product promotion, through labeling, advertising, marketing, and to restrict such product promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in any **shared digital properties** (e.g., your product-branded social media accounts, pages and associated content; content promoting your products on your behalf disseminated through another entity's social media accounts) – whether conducted by you, on your behalf, or at your direction – establish, maintain, and monitor use of the available site-, platform- and content-(e.g., post, video) specific age-restriction controls (e.g., age-restrict an entire product-branded account and all associated content disseminated through such account; ensure age-restriction of a specific video disseminated by an influencer promoting the products on your behalf through the influencer's account), at the first point of access to such properties in order to restrict access to such product promotion through labeling, advertising, marketing, and to restrict such promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products.

- For any of the products' labeling, advertising, marketing, and/or promotion appearing in **paid digital media** (e.g., paid digital banner advertisements for the product running on another company's website; paid advertising for the product running in social media; paid distribution of influencer content) – whether conducted by you, on your behalf, or at your direction:

    - Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies to precisely target delivery of such labeling, advertising, marketing, and/or promotion to only individuals who are at least of federal minimum legal age to purchase tobacco products. Such targeting must use only first- and/or second-party age-verified data, where:

        - "First-party" age-verified data is data owned by you (e.g., your customer registration data collected via site traffic to your company-owned website; data you use in direct

marketing to your adult smoking customers) that you have age-verified through independent, competent, and reliable data sources; and

- "Second-party" age-verified data is first-party data owned and age-verified by another competent and reliable entity (e.g., another company's first-party user registration data) to which you have access. Such data must be age-verified by the second party.

- "First-party" and "second-party" data does not include data obtained from data aggregators who categorize consumers based on trackable activities and inferred interests (e.g., internet search terms, video interactions, browsing history, purchasing behaviors) to create demographic and psychographic profiles marketers may use to enhance audience targeting. Such data is not considered age-verified and can only be used in combination with first- and/or second-party age-verified data.

- Establish, maintain, and monitor use of competent and reliable data sources, methodologies, and technologies (e.g., using an embedded tracking pixel in all digital advertising) – whether conducted by you, on your behalf, or at your direction – to **track and measure actual delivery of all advertising impressions**, by channel, by product, and by audience demographics (e.g., age, gender, race/ethnicity, geographic region). Such monitoring requires real-time digital media tracking, and identifying, correcting, and preventing delivery of advertising impressions to individuals under the minimum legal purchasing age. Such monitoring also requires post-launch delivery verification reports be submitted to you from an accredited source.

- For any use of **partners, influencers, bloggers, and/or brand ambassadors** to create labeling for, advertise, market, and/or promote the product – whether conducted by you, on your behalf, or at your direction – disclose to consumers or viewers, via the use of statements such as "sponsored by [firm name]" in such labeling, advertising, marketing, and/or promotional materials, any relationships between you and entities that create labeling for, advertise, market, and/or promote the product, on your behalf, or at your direction.

At any time, FDA may request that you provide any of the documents described in Appendix D. In addition, under section 704 of the FD&C Act, FDA may inspect your establishment(s) and request to inspect any record(s) described in Appendix D.

If you discontinue the manufacture, preparation, compounding or processing for commercial distribution of this tobacco product and later decide to reintroduce the products into the market, please contact the Office of Science prior to reintroduction. Also, every person who owns or operates any domestic establishment engaged in the manufacture, preparation, compounding, or processing of a tobacco product or tobacco products shall update their product listing biannually to reflect certain changes, including any products that have been discontinued and/or reintroduced into interstate commerce.